

In the Office Action summary, claims 5 is objected to but Applicant sees no discussion in the body of the action regarding any objection to claim 5. A review of claim 5 indicates that it is a proper claim dependent on claim 1 and should be acceptable as to form.

In the action, all claims of the application were rejected as unpatentable over Siebert et al. U.S. Patent 5,972,986 alone or in combination with other references including U.S. Patent 5,474,995 which discloses a specific COX-2 inhibitor, Rofecoxib, European Patent 0927555, U.S. Patent 5,641,755, and the publication by Milas et al. As applied to the claims as amended, these rejections are respectfully traversed and reconsideration is requested.

By this amendment, independent claim 1 is revised to be more specific with respect to the side effects, which can be alleviated by the method of the invention. Thus, claim 1 now recites the specific side effects disclosed in the specification and particularly at page 2, paragraph 06 and page 3, paragraph 13. In addition, new dependent claims 10-12 are added with support for these claims being found at page 7. Accordingly, no issue of new matter is raised and entry of the amendment is requested.

It is further submitted that the claims as amended are patentable over the prior art relied on by the Examiner. It is clear from all of the rejections that the main reference is the patent to Siebert et al. which relates to the use of cyclooxygenase-2 inhibitors in preventing and treating Neoplasia. Neoplasia is defined in the patent as being a Neoplastic disease state at column 1, lines 43-53, which is characterized by rapidly proliferating cell growth. None of these Neoplastic disease states however have anything to do with radiation treatment side effects. At column 2, lines 59-63, the patentee also

includes the sentence "The COX-2 inhibitors can also be used to treat the fibrosis which occurs with radiation therapy". This sentence is the total disclosure relied on in this patent as the basis for the Examiner's rejection of the present claims. It is submitted that this single statement in the sentence in column 2 is insufficient basis to justify the rejection and in any event, neither anticipates nor renders obvious the claims of this application.

As the Examiner will note, the claims are now amended to recite the specific side effects which can be treated according to the method of the invention by use of a cyclooxygenase-2 inhibitor. Fibrosis is not one of the disease states disclosed or claimed by Applicant. Further, fibrosis is a formation of excess fibrous tissue and as stated is not included in those disease states of claim 1. Therefore, the claims none of the claims are anticipated by Siebert et al.

It is further submitted that claim 1 is not obvious in view of Sibert et al. It is clear that the disclosure in Siebert et al. is simply a suggestion and not an "enabling disclosure" of the use of COX-2 inhibitors for the treatment of fibrosis which occurs with radiation therapy, because the reference does not teach how one treats fibrosis. In re Le Grice, 133 USPQ 365. The entire thrust of the Siebert et al. patent is directed to the use of COX-2 inhibitors to prevent and treat Neoplasia. The reference to the treatment of Fibrosis which occurs with radiation therapy has no other basis in the patent and therefore Applicant submits is a non-enabling disclosure based on this single sentence.

Further, the disclosure in Siebert et al. is clearly insufficient to suggest the method recited in Applicants' main claim 1 that COX-2 inhibitors can be used to treat the disease side-effects associated with radiation treatment as now recited in the claims. None of

these side-effects have anything to do with fibrosis. Fibrosis is defined in Webster's New Collegiate Diction, G.C. Merriam Co., page 422, (1980) and elsewhere, as the formation of interstitial fibrous tissue in excessive amounts. A copy of page 422 from Webster's New Collegiate Dictionary is enclosed. It is submitted that this teaching from this dictionary is sufficient to distinguish fibrosis resulting from any cause from the deleterious side-effects recited in Applicants' claim 1, and rebuts any presumption of obviousness raised by the Siebert et al. reference under 35 USC 103.

The basis of the original rejection apparently was that the language in Applicants' claims "deleterious side-effects" was sufficiently broad to be inherently accomplished by the use of a COX-2 inhibitor to treat fibrosis. Clearly, Applicants' amended claims are not subject to this interpretation so that the claims are no longer anticipated.

Further, Applicant submits that the claims are not obvious under 35 USC 103. There is no suggestion in Siebert et al. that COX-2 inhibitors would be effective to reduce the deleterious side effects resulting from radiation treatments which involve any of the side-effects recited in main claim 1.

The Examiner seeks to show that such side-effects would be obvious by the citation of secondary references such as European Patent 09/275,555, Weichselbaum et al. U.S. Patent 5,641,755, and the publication by Milas et al. In this rejection, the Examiner also points to the Siebert et al. disclosure at column 2, lines 1-6 wherein Siebert discusses conjunctive treatment of a selective COX-2 inhibitor with other neoplastic agents to produce a synergistic effect or alternatively reduce toxic side-effects associated with chemotherapy. However, chemotherapy with drugs is not what is being claimed in this application. Therefore, there is no equivalency between this section of

Siebert et al. and what is claimed in this application. Further, even Siebert et al. does not link this discussion of toxic side-effects associated with chemotherapy with the statement regarding treating fibrosis which occurs with radiation therapy. Therefore, the Examiner's attempt to connect these treatments is clearly insufficient as there is no motivation or suggestion contained in the patent that such statements are equivalent.

Further, there is no disclosure in the secondary references relied on by the Examiner that would make it obvious to one of ordinary skill in the art to extend Siebert's teachings to the deleterious side-effects recited in Applicants' claims in view of the secondary references. It is obvious from the discussion at pages 6, 7 and 8 of the Official Action that the Examiner has attempted to reconstruct Applicants' claimed invention based on these non-related disclosures in the secondary references. The Examiner relies on the European patent as teaching that a COX-2 inhibitor is a potent anti-inflammatory agent and has an inhibitory effect of cytokine production by inhibition of a pathway responsible for inflammation reaction. Weichselbaum is relied on as disclosing that inflammatory cytokines are responsible for radiation induced side-effects and inflammatory cytokine production is mediated by the same pathway. Milas is relied on as teaching the biological effects of prostaglandin and its production via the same pathway. The Examiner suggests that taking these references together, one would have been motivated to add selective COX-2 inhibitor into radiation treatment to reduce the deleterious side-effects. Applicant strongly disagrees on the ground that taking all these teachings together does not result in the invention as claimed.

The motivation found by the Examiner can only occur after one becomes aware of Applicants' teaching that side-effects caused by radiation can be effectively treated with

COX-2 inhibitors, and this is not a proper patentability standard. In re Lee, 61 USPQ 2d 1430. This case holds that the Examiner must find suggestions of obvious conclusions in the references themselves. He cannot use his own conclusions.

The fact is, the European patent discloses that COX-2 inhibitors can be used for the treatment and prevention of tumors, tumor related disorders and cachexia. Tumor related disorders do not include radiation treatment. Weichselbaum discloses that the addition of inhibitors of lipxygenase such as keto conazole, prior to irradiation, reduces the expression of tumor necrosis factor while maintaining the expression of other radiation induced genes. However, Weichselbaum does not disclose COX-2 inhibitors for any purpose. The European patent discloses COX-2 inhibitors but has nothing to do with radiation treatment. The publication by Milas is concerned with the enhancement of tumor response to gamma radiation by COX-2 inhibitors. This is not that same as treatment of side-effects resulting from radiation. The conclusion by Milas is that COX-2 inhibitors can possibly potentiate tumor response to radiation or in other words, improve the treatment. There is no discussion or suggestion regarding treatment of side-effects resulting from radiation.

The references therefore contain a number of unrelated teachings which do not result in the claimed invention based on the teachings of the references themselves.

As pointed out above, Applicants strongly disagree that there is motivation to be found in the references themselves to combine them to result in the invention claimed herein.

In further support of Applicants' position, submitted herewith is a Declaration Under 37 CFR 1.132 by Dr. Ralph R. Weichselbaum, one of the inventors in this

application, the lead inventor named in U.S. Patent No. 5,641,755, one of the references relied on by the Examiner, and one of skill in the art. In this Declaration, Dr. Weichselbaum clearly refutes the Examiner's suggestions of obviousness of the claims in this application based on the reference teachings and their combination. It is submitted that this Declaration is clear evidence that the claims are not obvious in view of the prior art and overcomes the Examiner's suggestions of motivation based on these references.

As pointed out by the Board of Patent Appeals and Interferences in Ex Parte Levengood, 27 USPQ 2d 1306, an Examiner cannot establish obviousness through references describing various aspects of Applicant's invention unless the Examiner also provides evidence of a motivating force to impel a person skilled in the art to do what Applicant has done. Clearly, that is not the case here. As noted in In re Antonie, 915 USPQ6, the prior art must contain some suggestion of the desirability of making the proposed modification. Here the Examiner is attempting to show a link between the teachings of these references through her own knowledge after having read Applicants' specification. This is specifically indicated by the Court of Appeals for the Federal Circuit as an improper standard of patentability. As pointed out in In re Lee, supra, a recent Federal Circuit case, the Examiner must find the suggestions of obvious conclusions in the references themselves. The Examiner cannot use his own conclusions based on the disclosure presented to him by an Applicant. Therefore, the Examiner's attempt to link these several prior art references through the discussion of the prostaglandin/arachidonic pathway responsible for an inflammation reaction is clearly barred as a way of finding motivation by the Patent Office Board of Appeals and the Courts and is also rebutted by the newly submitted Weichselbaum Declaration.

Further, the Examiner's conclusion on page 6 of the Official Action that "it would have been obvious to one of ordinary skill in the art to extend Siebert's teaching" to the side-effects recited in Applicants' claims by modification of the secondary references, it appears to be "an obvious to try" test which has also been barred by the Courts as a patentability standard under 35 USC 103. See In re Thomlinson et al., 150 USPQ 623 and In re Yates, 211 USPQ 1149.

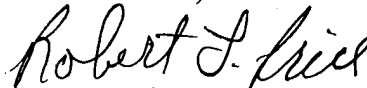
For these reasons, it is submitted that the claims as amended in this application are clearly novel and unobvious under 35 USC 103. Accordingly, reconsideration and early allowance are believed to be in order.

Attached hereto is a marked-up version of the changes made to the specification and the claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**".

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

MCDERMOTT, WILL & EMERY



Robert L. Price

Registration No. 22,685

600 13<sup>th</sup> Street, N.W.  
Washington, DC 20005-3096  
(202) 756-8000 RLP:ajb  
Facsimile: (202) 756-8087  
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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**IN THE CLAIMS:**

Claim 1 has been amended as follows:

1. (Amended) A method of reducing one or more deleterious side [effect] effects of radiation treatment in a subject undergoing radiation treatment, the side effects being one or more of those selected from the group consisting of acute mucosal effects on the urinary or gastrointestinal tract, fatigue, diarrhea, rectal bleeding, proctitis, sigmoiditis, urinary frequency, prostatitis, cystitis, dermatitis, pneumonitis, large bowel irritation, small bowel irritation, nausea and vomiting, comprising administering to said subject a side-effect reducing amount of a selective cyclooxygenase-2 inhibitor.